

JAPANESE MEDICAL MATERIAL

PYRISULFON

(Disodium 5-aminopyridyl-2, 4'-aminophenyl-sulfone-diglucosesulfonate)

297198

Report No. 239

1 July 1946

MEDICAL ANALYSIS SECTION  
5250th Technical Intelligence Company  
APO 500

## PYRISULFON

(Disodium 5-aminopyridyl-2, 4'-aminophenyl-sulfone-diglucosesulfonate)

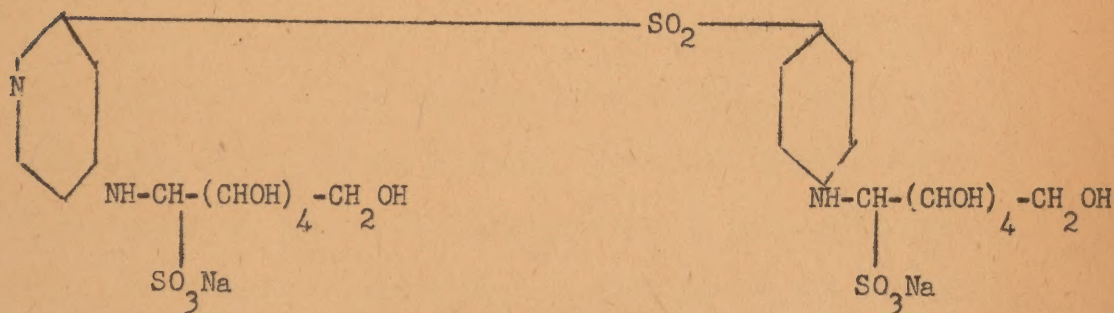
SOURCE: Tokyo, Japan

IMPORTANCE: Not previously reported. A soluble synthetic organic sulfone which is the mono-yrityl analogue of the American product, Promin, and is intended for use in tuberculosis and malaria. No identical chemical is listed in available standard American references.

DESCRIPTION: Ten amber-colored ampuls containing approximately ten cc. of a clear solution are enclosed in a cardboard box.

### SUMMARY OF GENERAL INFORMATION:

Chemically, Pyrisulfon is the disodium salt of 5-aminopyridyl-2, 4'-aminophenyl-sulfone-diglucosesulfonate with the following structural formula:



The pure chemical is described as a hygroscopic, white powder which is soluble in water but insoluble in ether and alcohol.

Pyrisulfon base (5-aminopyridyl-2, 4'-aminophenylsulfone) has been employed in experimental pneumonia (types I, II, and III) in animals under the name of Pyridinin. It is claimed that the response, with fewer secondary reactions, was more favorable than that obtained from sulfathiazole and sulfapyridine. Mention is also made that the base has been employed for tubercular patients. that it is an excellent antipyretic, but details are lacking.

Pyrisulfon is recommended for tuberculosis and malaria, and the initial oral, maintenance oral and intravenous doses are recorded. The minimum lethal dose of Pyrisulfon for mice is given as 160 mg. as compared to 100 mg. for Promin; greater toxicological safety is thus claimed.

A translation of the literature enclosed with Pyrisulfon is part of this report and includes its chemistry and description, cautions, indications, dosage and manufacturer. Additional literature furnished by the manufacturer has also been translated and included in this report thereby furnishing some information on certain pharmacological and toxicological tests, as well as an outline of the method of synthesis

In view of the tremendous number of sulfonamide and sulfone compounds which have been synthesized and pharmacologically investigated in recent years, evaluation of this product can be made only after a literature search in the zone of the interior.

PHOTOGRAPHS:

Figure 1 - Closed package of Pyrisulfon

Figure 2 - Open package of Pyrisulfon

Figure 3 - Pyrisulfon literature

Figure 4 - Pyrisulfon literature

Figure 5 - Pyrisulfon literature

Figure 6 - Pyrisulfon literature

Figure 7 - Additional Pyrisulfon literature

Figure 8 - Additional Pyrisulfon literature

Figure 9 - Additional Pyrisulfon literature

Figure 10 - Additional Pyrisulfon literature

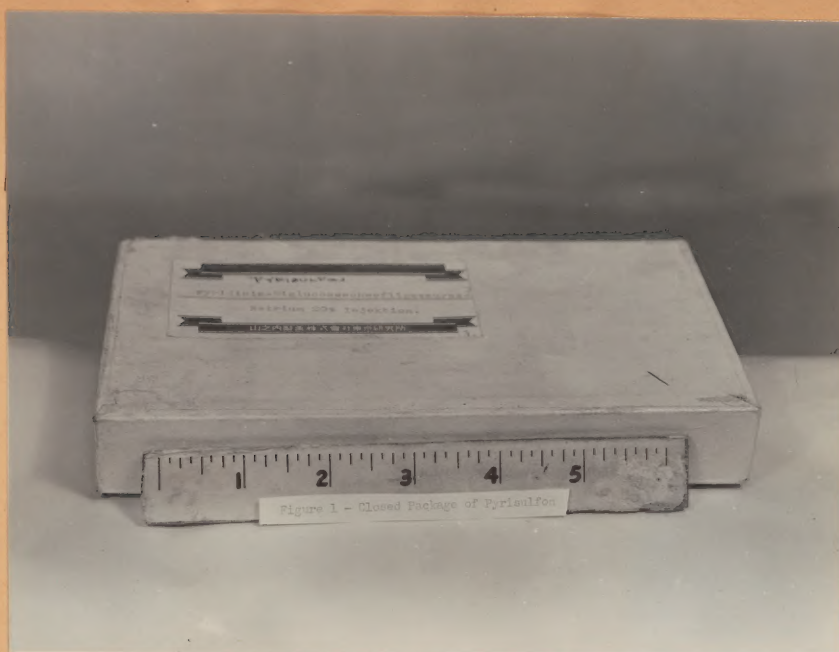


Figure 1 - Closed Package of Pyrisulfon



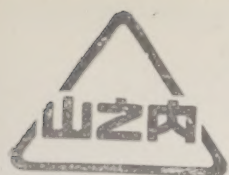
Figure 2 - Open Package of Pyrisulfon

PYRISULFON<sup>BC</sup>

# ピリスルフォン 注射液



山之内製薬株式会社



# ピリスルフォン注射液

## Pyrisulfon

### 概

### 説

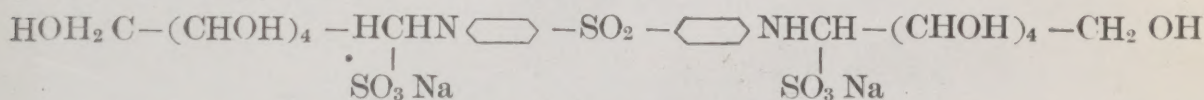
Trefauel Nitti 及び Bouet 氏等はスルフォンアミド化合物が化學療法的作用を發現するにはスルフォンアミド基がアミノ基のパラ位に存在せねばならぬとの事實を立證して以來、幾多の所謂ズルフオンアミド系誘導體が發明された。然るに 1937年 Buttle 及び Fourneau 氏一派に依り之と全く異なるデフェニールズルフオン誘導體 (= N- $\langle \rangle$ SO<sub>2</sub>- $\langle \rangle$ -N) がズルフオンアミド誘導體に比し抗菌作用遙かに強力なることが發見されズルフオンアミド基 (-SO<sub>2</sub>NH) に對してスルフォン基 (-SO<sub>2</sub>-) が主要なる抗菌性因子であることが想像されるに至つた。我國に於ては醫學博士森澤清氏が Buttle 及び Fourneau 氏等とは別個に獨自の構想に基く異項環系スルフォン誘導體に着眼し既に 1937 年數多の合成研究に成功した。

就中、之等誘導體中ピリデン系スルフォン化合物たるピリデニンは 5-Aminopyridyl (2) - 4' aminophenyl-sulfon にして H<sub>2</sub>N $\langle \rangle$ SO<sub>2</sub> $\langle \rangle$ NH<sub>2</sub> なる構造式を有し肺炎菌 I, II, III, 型菌感染獸に對する實驗の結果、從來最も効果的とされてゐたスルファピリデン、スルファチアツオール等に比し遙かに強力なる作用を有し、副作用極めて僅少な事が明らかにされた。

(衛生試験所彙報 No. 56 醫學博士秋葉朝一郎氏東京醫事新誌 No. 3187)

又臨床的には東京帝國大學助教授鹽澤總一博士及び東京慈惠會醫科大學教授加藤義夫博士等に依り本劑の眞價は愈々認められるに至つた。

然しその後米國に於てはデフェニールスルフォン誘導體に關し異常なる研究が続けられ遂に 1941 年 Hinshaw 及び Feldman に依り p-p' Diamino diphenyl sulfon di-glucose schwefligsaures natrium



を合成し Promin と名付けた、本化合物は實驗的海豚結核に對し劃期的著効を立證せられ結核の化學療法に一大光明を與へるものと期待されるに至つた。

因みに 1941 年の Jour. Amer. Med. Ass. に於ける發表に依れば彼等は海狸に人型結核菌を

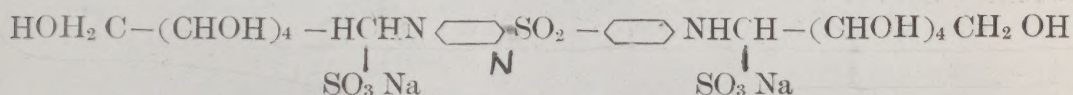
0.0005mg 接種し、これを八群に分け夫々菌接種の2日前、前日、3日後、7日後、2週後、4週後及び六週後から食餌に1%の割合にプロミンを混ぜ與へた。プロミンの量は各動物共1日量300~400mgである。對照群の最後の動物が死亡したのは菌接種後189日目であつたがこの時にはプロミン投與群は尙84%元氣に生存しをり、又此の時迄に死亡したプロミン投與群動物には肉眼的に識別出来る様な内臓結核の發生を見たのは1匹もなかつた。

菌接種後192日目に全部殺して剖検した結果プロミン投與群動物の60%には肉眼的に見別けられる結核嚢形成が無く、僅か3匹(4%)にのみ内臓結核の發生が肉眼的に見られたが廣泛な結核病變の見られたものは1例もなかつた。

菌接種後、4週間、6週間、を経てからプロミン投與を開始した動物でも、他の動物と全く同様に、完全に近い結核進展抑制効果が見られた事實には、實驗者自身も驚いてゐる程である。檢鏡所見ではプロミン投與群の59%は前存生又は不活動性の病變で、海狸結核に於ては殆んど見られないような所見であつた。即ち、乾酪變性は全く缺如し、フィブローズが盛で結締組織による病竈區割作用が著しく、然もかゝる短時日のうちに石灰化嚢が屢々見られたのは驚くべき事である。

而して Mayo 一派に依り臨床實驗が繼續せられてゐるがその効果に就ては結論的な發表をする迄に至つてゐない。

一方我國に於ては醫學博士森澤清氏が Hinshaw 及び Feldman とは全々異なり自からの創成になる前記ピリヂニンより唆示を得て 2601 年遂に 5-Aminopyridyl (2)-4' aminophenyl sulfon diglucose schwefligsaures natrium



の合成に成功した。

而して本化合物の前身たるピリヂニンに於ては既に東京慈恵會醫科大學加藤義夫教授に依り肺結核に使用されてゐる(東西醫學第9巻第10號昭和17年10月)

即ち重症肺結核患者にして高度の弛張熱を示し他の總ての下熱劑にて効を奏せざりし數例に於て1日1.0~1.5瓦投與にてその悉くが2~3日にて消失してゐる。この異常な著効には注目すべきものがある。

而して Hinshaw 及 Feldman の言の如く糖類を結合することにより飛躍的に治効作用を發揮し得るのは糖類の存在が單に溶解性を賦與せしめる爲ばかりでなく強力な抗菌作用發現に對して他に何か重大なる意義ある如く思はれる。

然も Promin に於ては18gのマウスにて試験したるに最少致死量は100mgであるが本化合物は同條件のもとで最少致死量は160mgにして副作用は著しく少くなつてゐる

即ち Promin は大量を長期間に亘つて用ひる時は間々溶血性貧血が起りヘモグロビン量は低下し、著明な赤血球再生像が見られるが本化合物に於てはより大なる忍容量を有する故結核の如き長期間に亘つて使用せねばならぬ場合本品の偉力は誠に絶大なるものがある。

## 性 狀

上記の化學構造を有し、白色粉末、水に可溶、エーテル、アルコールに不溶にして分解點 89° C なり。特に吸濕性甚しく貯藏には乾燥劑を必要とする。

## 使 用 時 注 意

- 1、本劑と硫酸鹽及硫化物との併合はメトヘモグロビン或はズルフオヘモグロビン血症を起すことあり注意を要す。
- 2、本劑と銀、水銀製劑及びアニリン系藥物類との併用はアグラスロチトーゼの如き副作用を伴ふ場合あるに依り併用を避けられ度し。
- 3、本劑と酸及アルカリとの併用は分解を起す恐れある故避けられ度し。

## 應用範圍及び使用量

肺結核、腎臟結核、皮膚結核、結核性腦膜炎等に對しては1日1.8瓦より漸次増量3.2瓦乃至4瓦を4回に投與す。

注射は20%を1日1回靜脈内注射す。マラリヤに對しては1日4瓦以上8瓦を4回に投與す。

内服は食後1時間半乃至2時間内に服用するを推奨す。

## 山 之 内 製 藥 株 式 會 社

東京都日本橋區小舟町二丁目三番地  
大阪店・大阪市東區高麗橋五丁目十九番地  
臺北店・北京店・廣東店・香港店

## 山之内製藥株式會社東京研究所

東京都本郷區金助町三八番地

## 滿洲山之内製藥株式會社

奉天市大和區紅梅町二番地

## 上海山之内製藥株式會社

上海百老匯路二六三號

内服は食後 1 時間半乃至 2 時間内に服用するを推奨す。

[ Diamino pyridyl phenylsulfon の毒性及効果に関する總括 ]

Dipyridyl sulfon 誘導体 2 種及び Pyridyl phenyl-sulfon 誘導体 2 種に就き其の肺炎双球菌 I. II. III 型及び溶血性連鎖状球菌感染に對する治效力を試験したる結果を總括すれば次の如し。

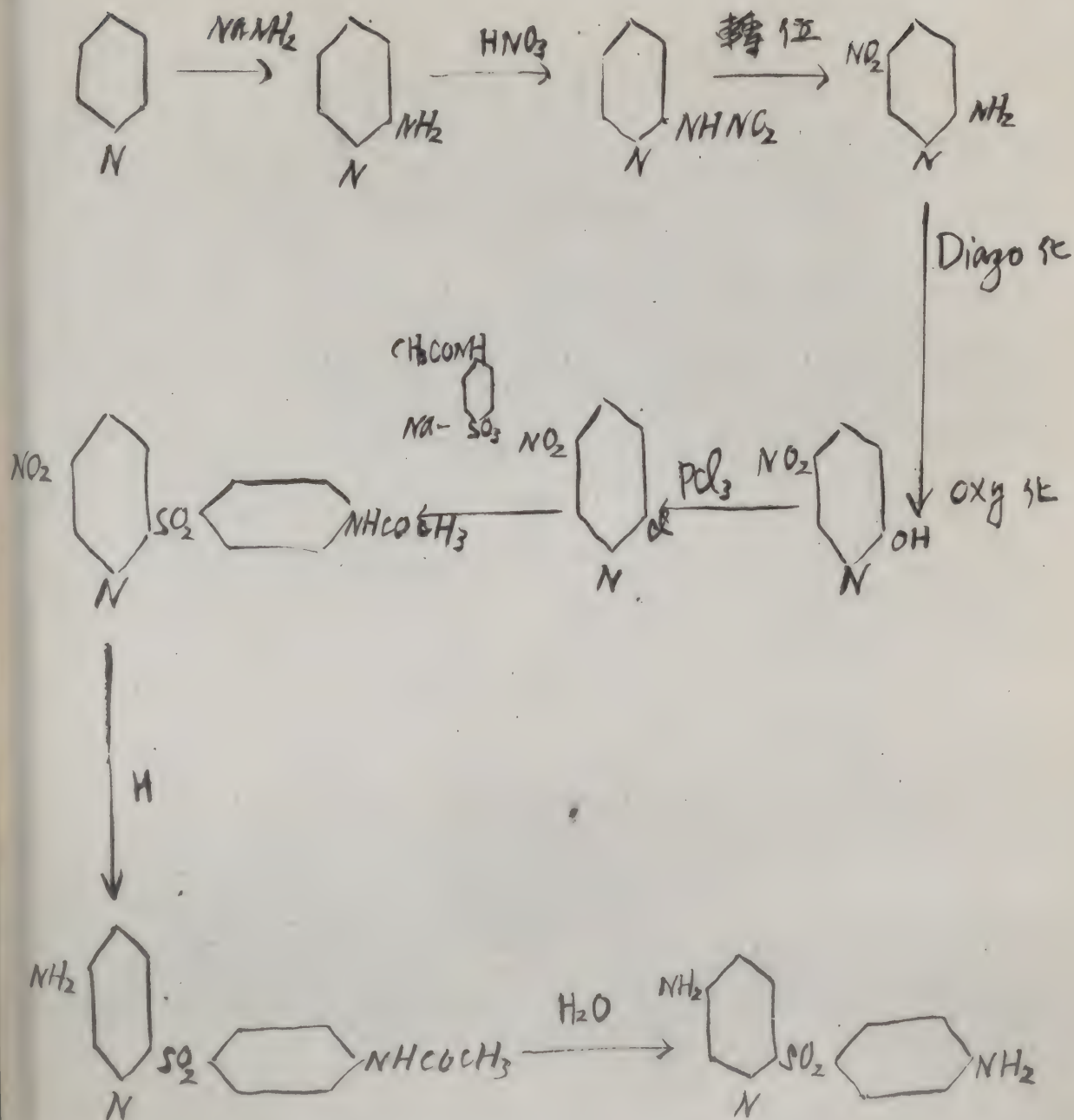
1. Dipyridyl sulfon 誘導体 2 種の效果は pyridyl phenyl sulfon 誘導体 2 種の效果に劣る。
2. Pyridyl phenylsulfon 体中 5-Nitro pyridyl - (2) - 4' - nitro phenylsulfon (5-nitro pyridyl phenylsulfon) は 5-Amino pyridyl - (2) 4' - Amino phenyl-sulfon (Diamino pyridyl phenylsulfon)

よりも肺炎双球菌感染に對する效果微弱なり。

3. Diamino pyridyl phenylsulfon は肺炎双球菌 I 型及び II 型菌に對しては salzapyridin に優る效果を示すも III 型菌に對しては I 及び II 型菌に對する程效果著しからずして salzapyridin と略々同等の效果を示せり。

4. *5-nitropyridyl phenylsulfon* 及び *5-amino pyridyl-phenylsulfon* の 2 種は連菌感染に對し肺炎双球菌に對するよりも一層強い効果を示し其の程度は *sulfanilamid* 及び *Diseptal* と同等なるとも *sulfapyridin* に比すれば之に劣る。
5. 經口投與によるマウスに對する毒性は *5-nitro-Pyridyl phenylsulfon* は *sulfanilamid* より弱く *sulfapyridin* と同様なり 之に反し *5-amino pyridyl-sulfon* は *sulfanilamid* よりも毒性強きも尙 *Prontacil rubrum* よりは弱し。

セビリチルズルフォン



Pyridin を Xylol 又は Toluol に溶解し  $\text{Na-NH}_2$  を作用せしめて 2-Amino pyridin を生成し濃硫酸に溶解し冷時昇煙硫酸を作用させて Nitroamino-Pyridin を生成す。

次は之に硫酸を加へ加温して轉位せしめ、水蒸氣蒸溜により 3-Nitro-2Aminopyridin と分離して 5-Nitro 2Aminopyridin を得、之を硫酸に溶解し亜硫酸ソーダを作用して Diazo 化し稀硫酸と煮沸して 5-Nitro 2oxy pyridin を作り  $\text{PCl}_3$  を作用せしめて 5-Nitro-2chlor-Pyridin を生成する。

次で p-Acetaminobenzenesulphin 酸ソーダとアルコール中に加温して p-Acetaminophenyl 5-nitro-Pyridyl sulfon を得、還元し次で加水分解して Pyridylsulfon を得る。

## 2) N-Glucose sulfonat の生成

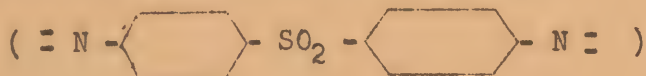
前記の Aminophenyl Amino pyridin を 1Mol と 2Mol の Glucose を Alcohol 中に加熱溶解し Alcohol を蒸溜し去つて sulfon N-glucosid を得、之に 2Mol の  $\text{NaHCO}_3$  (新に調製せるもの) 溶液を加へて溶解し水分を真空蒸發して結晶粉末を得。

# Translation of Accompanying Literature

## PYRISULFON

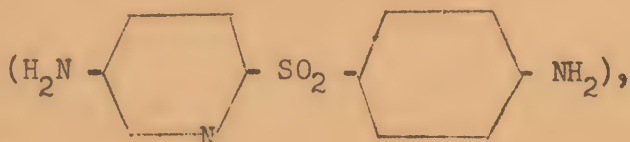
### General:

Since Trefouel, Nitti and Bouvet proved that only "para" sulfonamides are chemotherapeutically active, many such derivatives have been synthesized. In 1937, Buttle and Fournau discovered that "diphenyl sulfone" derivatives



are far more powerful than sulfonamide derivatives. It is believed that the sulfone (  $-\text{SO}_2-$  ) radical is the active part of the diphenyl sulfone derivatives, just as the sulfamide radical (  $-\text{SO}_2\text{NH}$  ) is the active part of the sulfonamides.

In Japan, Dr. Morisawa, working independently from Buttle and Fournau, paid special attention to pyridine-sulfone and completed many such synthetics by 1937. Among these was 5-aminopyridyl-(2) -4' aminophenyl sulfone,

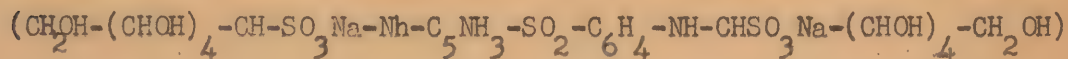


which he called "Pyrydinin". Tests proved that animals infected with types I, II, and III pneumococci responded more favorably with this compound and showed less secondary action was noticed in comparison with sulfathiazole and sulfapyridine. (Sanitary Laboratory Report No. 56, Tokyo Medical Affairs New Magazine No. 3187 by Dr. Asaichiro Akiba).

The clinical value of this drug has been proved by Dr. Soichi Shiozawa, an assistant professor at Tokyo Imperial University, and by Dr. Yoshio Kato, professor of the Tokyo Charity Association Medical College.

In the United States, Hinshaw and Feldman (1941) developed p-p'-diamino-diphenyl-sulfone-diglucose-sulfonate sodium and called it promin. Beavers, inoculated with tuberculosis, were the test animals and good results were obtained by treatment with promin. (cf. Journal American Medical Association 1941). Mayo and followers are now carrying on clinical experiments but at the present time too limited tests have been carried out for accurate conclusions.

Then, Dr. Kiyoshi Morisawa succeeded in synthesizing 5-amino-pyridyl-(2) - 4' aminophenyl-sulfone-diglucose sodium



Dr. Katto also used "Pyrydinin" on tubercular patients and reported his conclusions in the Western and Eastern Medical Science Vol. XI No. 10, October 1942.

The following is quoted from this report:

"Other Antipyretics were not effective against the high fever of the serious tubercular patient. Then I used "Prydinin" prescribing from 1.0 to 1.5 grams of it every day, and the patient lost the fever in a few days. Thus, the extraordinary effect of Prydinin is quite surprising".

While the promin M.L.D. (mouse test) is 100 mg., this medicine necessitates the use of 160 mg., which means less secondary reactions are present. In other words, promin causes anemia when used for long periods such as are needed in tubercular medication.

#### Description:

The formula is mentioned above. It is a hygroscopic white powder, soluble in water but insoluble in ether or alcohol. It melts at 89° C.

#### Caution:

Sulfates, sulfides, silver and mercurial salts, and aniline derivatives, must not be prescribed with this medicine since agranulocytosis and other dangerous reactions will occur. Acids and alkalis cause decomposition of this medicine.

#### Indications and dosages:

Pyrisulfon may be used in tuberculosis of various parts of the body. 1.8 gm. of pyrisulfon is divided into four doses for the first day of treatment. The daily dose is then gradually increased to 3.2 to 4.0 gm, and is given in four doses. If intravenous injection is desired, give 20% of this amount once a day. As a malaria remedy, give four equal doses totaling from 4 - 8 grams daily. Oral medication should be given one or two hours after meals.

#### Manufacturer:

Yamanouchi Pharmaceutical Co., Ltd.  
No. 3, 2-Chome, Kofune-cho,  
Nihonbashi-Ku, Tokyo.

Osaka Branch  
No. 19, 5-Chome, Koraibashi, Higashi-Ku, Osaka.

Taihoku Branch, Peipin Branch, Kwantang Branch,  
Hongkong Branch.

Tokyo Laboratory of the Yamanouchi Pharmaceutical Co.,  
No. 38, Kanasuke-cho, Hongo-Ku, Tokyo,

Manchuria Yamanouchi Pharmaceutical Co.,  
No. 2, Kobai-cho, Yamato-Ku, Hoten City

Shanghai Yamanouchi Pharmaceutical Co.,  
No. 263, Bailaohui-Lu, Shanghai

TRANSLATION OF ADDITIONAL DATA AS SUPPLIED BY MANUFACTURER

PYRISULFON

(Summary of the toxicity and effects of  
Diamino pyridyl phenylsulfone)

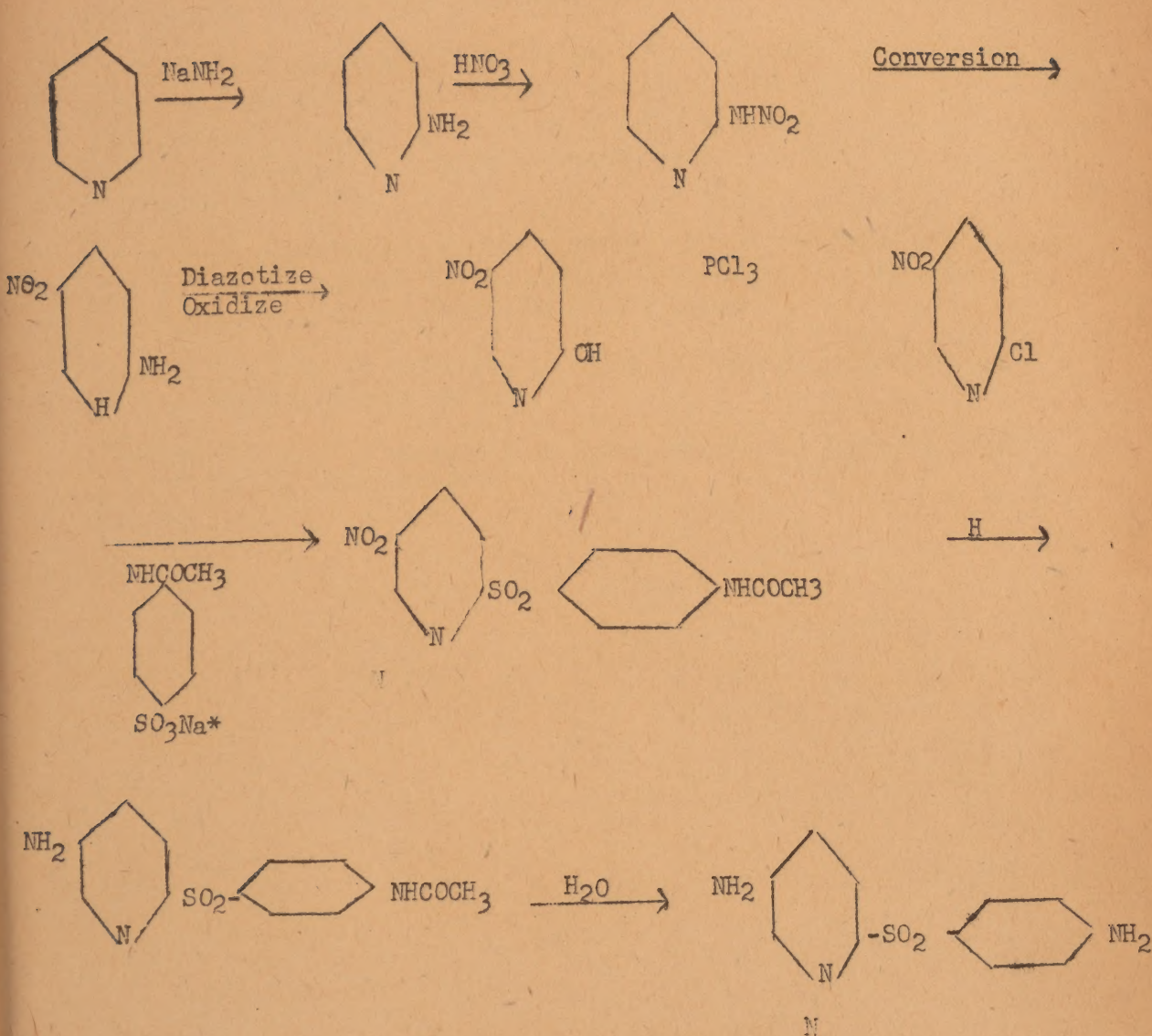
A summary of the results derived after testing the effect of the two types of Dipyrldyl sulfone derivatives and two types of Pyridyl phenylsulfone derivatives against pneumococcus Types I, II, III and hemolytic streptococcus infection follows.

1. The effects of two types of Dipyrldyl sulfone derivatives are inferior to that of pyridyl phenyl sulfone.
2. Of the Pyridyl phenylsulfones, 5-nitro pyridyl-(2)-4'-Nitro phenylsulfone (Dinitro pyridyl phenylsulfone) is less effective against pneumococcus infection than 5-aminopyridyl-(2) 4'-amino phenyl sulfone (Diamino pyridyl phenylsulfone).
3. Although Diamino pyridyl phenylsulfone shows a superior effect against pneumococcus Type I and II than Sulfapyridine, it is not as effective against Type III and its effect is almost identical with that of Sulfapyridine.
4. The two types of Dinitro pyridyl sulfone and Diamino pyridyl phenylsulfone are more effective against streptococcus infections than against pneumococcus infections. Their degree of effectiveness is the same as that of Sulfanilamide and Diseptol but inferior to that of Sulfapyridine.
5. When administered orally to a mouse, the toxicity of dinitro pyridyl phenylsulfone is less than that of Sulfanilamide and the same as that of Sulfapyridine. In contrast to this, the toxicity of diamino pyridyl sulfone is greater than Sulfanilamide but less than that of Prontosil Rubrum.

cf. Report of Sanitary Laboratory, Vol. 56, p. 12-18.

# SYNTHESIS OF PYRISULFON

(PYRIDYLSULFON)



Dissolve the pyridine in xylol or toluol and add Sodamide to get 2-aminopyridine. Dissolve this in concentrated sulfuric acid and add fuming sulfuric acid\*\* in a cold state to produce nitro amino pyridine.

Then convert this by adding sulfuric acid and heating it. Separate the 3-nitro-2-aminopyridine by steam distillation and obtain the 5-nitro 2-amino pyridine. Dissolve this in sulfuric acid, diazotize in the presence of sodium sulfite, boil with dilte sulfuric acid, and obtain 5-nitro 2-oxypyridine. Add  $\text{PCl}_3$  to get 5-nitro-2-chlorpyridine.

Heat this with Sodium p-acet-aminobenzenesulphinate and alcohol and obtain p-acetaminophenyl-5-nitro-pyridyl-sulfone and then produce the pyridyl-sulfone by reduction and hydrolysis.

#### PREPARATION OF N-GLUCOSE SULFONATE,\*\*\*

Heat and dissolve 1 mol. of the above aminophenyl-amino-pyridine and 2 mol. of Glucose in alcohol, distill the alcohol and obtain the sulfone-N-glucoside. To this add 2 mols. of  $\text{NaHCO}_3$  (freshly prepared) Solution, vaporize the water by vacuum evaporation and retain the crystalline powder.

\* This is evidently an error and should probably be the " $\text{SO}_2\text{Na}$ " group inasmuch as the description refers to this compound as SODIUM p-ACET-AMINOBENZENE-SULPHINATE.

\*\* T.N. This is evidently an error and should probably read "fuming nitric acid".

\*\*\*\* T.N. This is evidently an error and should probably read "NN-GLUCOSE-SULFONE".